Citation:

Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, Tsugane S; JPHC Study Group. Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: The Japan Public Health Center-based (JPHC) study cohort I. *Circulation*. 2007 Nov 27;116(22):2553-62.

PubMed ID: 18025534

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

The purpose of this study was to identify if the risk of cerebral infarction (CI) and myocardial infarction (MI) was reduced through exposure to a large quantity of isoflavones.

Inclusion Criteria:

This study included men and women from Cohort I of the Japan Public Health Center-Based (JPHC) Study, a population-based sample of 27,063 men and 27,435 women born between 1930 and 1949 (between 40 and 59 years old) who had given informed consent.

Exclusion Criteria:

Subjects who reported MIs, angina pectoris, strokes or cancer before the study.

Description of Study Protocol:

Recruitment A self-administered questionnaire (including demographics, medical history, smoking and drinking habits, and diet) was distributed to all registered noninstitutional residents in 1990. The 40,462 people who returned their questionnaires between January 1990 and May 1992, and met the inclusion criteria, were included.

Design: Prospective cohort study

- The 1990 food-frequency questionnaire included 44 foods with 3 questions to assess soy, bean, and miso consumption. A 1995 follow-up questionnaire covered 147 foods with 8 questions on soy products, including serving sizes. Isoflavone intake was calculated.
- Portion size and isoflavone contents were validated through a correlation study in which 247

subjects provided 28-day dietary records accompanied by blood and urine samples.
- Stroke and MI were confirmed and classified using standard criteria from medical records by PCH physicians who did not have access to lifestyle data. Fatal stoke and MI were identified by death certificates.

Blinding used (if applicable) Not described.

Intervention (if applicable) Not applicable

Statistical Analysis

- ANOVAs and x^2 tests were used to compare mean values and frequencies of dietary soy intake by sex.
- Time-dependent Cox proportional hazards regression models were used (adjusted for confounding variables such as age, smoking, alcohol intake, BMI, hypertension, diabetes, medications, dietary intake, and sports activities) for the association of soy, miso soup, beans, and isoflavones with CI and MI.

Data Collection Summary:

Timing of Measurements

The first questionnaire was distributed in 1990 and completed through 1992. A follow-up questionnaire was distributed in 1995. Outcomes were measured through January 2003.

Dependent Variables

- MI and stroke (classified by physicians from medical records using standard criteria)
- Stroke and MI were confirmed and classified using standard criteria from medical records by PCH physicians who did not have access to lifestyle data. Fatal stoke and MI were identified by death certificates.

Independent Variables

- Intake of isoflavones, soy and beans
- The 1990 food-frequency questionnaire included 44 foods with 3 questions to assess soy, bean, and miso consumption. A 1995 follow-up questionnaire covered 147 foods with 8 questions on soy products, including serving sizes. Isoflavone intake was calculated.
- Portion size and isoflavone contents were validated through a correlation study in which 247 subjects provided 28-day dietary records accompanied by blood and urine samples.

Control Variables

- Age
- Smoking
- Alcohol intake
- BMI
- Hypertension
- Diabetes
- Medications
- Dietary intake
- Sports activities

Description of Actual Data Sample:

Initial N: 27,063 men and 27,435 women

Attrition (final N): 40,462 in the analysis

Age: 40 to 59 years old

Ethnicity: Japanese

Other relevant demographics: Several districts of Japan were included

Anthropometrics: no significant differences in BMI

Location: Japan

Summary of Results:

Key Findings

- After 503,998 person-years of follow-up, there were 587 cases of CI and 308 cases of MI and 232 cases of mortality for CI and MI combined.
- Subjects who ate more soy were slightly older and a lower education level, were less likely to smoke, more likely to be hypertensive, and the men were more likely to have diabetes mellitus. Frequency of soy intake was positively associated with total energy intake and with daily intake of rice, vegetables, fruits, and fish.
- For women, the multivariate hazard ratios for those consuming soy ≥5 times per week compared to those consuming soy 0 - 2 times per week was 0.64 (95% CI: 0.43, 0.95; P for trend=0.037) for CI, 0.55 (95% CI: 0.26, 1.09, P for trend=0.098) for MI, and 0.71 (95% CI: 0.49, 1.01, P for trend=0.065) for CI and MI combined.
    - No signficiant association between intake of miso soup or beans with CI or MI was observed among women.
- For men, there was no significant association between dietary intake of soy, miso soup, or beans with CI or MI.
- The multivariable HR for those who consumed soy foods ≥5 days per week compared with 0 to 2 days per week was 0.31 (95% CI: 0.13, 0.74; P for trend=0.006) for ischemic CVD mortality in women, but no association was found in men.
- No significant associations between intake of miso soup and beans and ischemic CVD mortality were present in either men or women.

Significant HRs (95% CIs) for the Incidence of CI and MI by Dietary Intake of Women of Soy and Beans

Soy, days per week	0-2	3-4	≥ 5	P for Trend
CI (multivariable)	1	0.81 (0.55-1.19)	0.64 (0.43-0.95)	0.037
MI (age-adjusted)	1	0.61 (0.31-1.18)	0.45 (0.23-0.88)	0.024
CI and MI (age-adjusted)	1	0.73 (0.53-1.00)	0.64 (0.47-0.87)	0.008
Beans, days per week				

CI (age-adjusted)	1	0.75 (0.56-1.00)	0.62 (0.39-0.97)	0.018
CI and MI combined (age-adjusted)	1	0.83 (0.64-1.06)	0.65 (0.43-0.97)	0.022

Significant Multivariable HRs (95% CIs) for the Incidence of CI and MI by Dietary Intake of Women

Quintiles of Isoflavone Intake

	Q1	Q2	Q3	Q4	Q5	P for Trend
CI	1	0.53 (0.33-0.84)	0.48 (0.30- 0.78)	0.55 (0.35- 0.87)	0.35 (0.21-0.59)	0.015
MI	1	0.78 (0.38-1.59)	0.46(0.20-1.07)	0.30 (0.11-0.79)	0.37 (0.14-0.98)	0.006

Author Conclusion:

An inverse association, especially in post-menopausal women, between soy and isoflavone intake and risk of incidence for CI, MI, and CVD mortality, was found. Soy contains high linoleic acid and vitamin E and may reduce the risk of MI primarily due to its serum cholesterol-lowering effect. While the study included a large number of subjects, the intake of isoflavones in the 2nd quintiles of isoflavone intake were 20 times higher than the mean levels of isoflavone intake in Westerners.

Reviewer Comments:

Dietary intake measured at baseline with a general FFQ not specifically addressing soy food intake. Authors note that the isoflavone intake of subjects in the 2nd quintiles of intake was 20 times higher than mean intake of Westerners, limiting generalizability to other ethnic groups.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes

| 4. | | Is the intervention or procedure feasible? (NA for some epidemiological studies) | Yes |

Validity Questions			
1.		**Was the research question clearly stated?**	Yes
	1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
	1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
	1.3.	Were the target population and setting specified?	Yes
2.		**Was the selection of study subjects/patients free from bias?**	Yes
	2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
	2.2.	Were criteria applied equally to all study groups?	Yes
	2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
	2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.		**Were study groups comparable?**	Yes
	3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
	3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
	3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
	3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
	3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
	3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.		**Was method of handling withdrawals described?**	Yes

4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A

7. **Were outcomes clearly defined and the measurements valid and reliable?** `???`

7.1.	Were primary and secondary endpoints described and relevant to the question?	`Yes`
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	`Yes`
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	`Yes`
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	`???`
7.5.	Was the measurement of effect at an appropriate level of precision?	`Yes`
7.6.	Were other factors accounted for (measured) that could affect outcomes?	`???`
7.7.	Were the measurements conducted consistently across groups?	`Yes`

8. **Was the statistical analysis appropriate for the study design and type of outcome indicators?** `Yes`

8.1.	Were statistical analyses adequately described and the results reported appropriately?	`Yes`
8.2.	Were correct statistical tests used and assumptions of test not violated?	`Yes`
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	`Yes`
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	`N/A`
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	`Yes`
8.6.	Was clinical significance as well as statistical significance reported?	`Yes`
8.7.	If negative findings, was a power calculation reported to address type 2 error?	`N/A`

9. **Are conclusions supported by results with biases and limitations taken into consideration?** `Yes`

9.1.	Is there a discussion of findings?	`Yes`
9.2.	Are biases and study limitations identified and discussed?	`Yes`

10. **Is bias due to study's funding or sponsorship unlikely?** `Yes`

10.1.	Were sources of funding and investigators' affiliations described?	`Yes`
10.2.	Was the study free from apparent conflict of interest?	`Yes`